

Exhibit 4

**Notice on the Results of the Report of the Preliminary Investigation on the Formation of
Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan**

Jinsheng LIN

To: Jucai GE, Tianpei HUANG, Wangwei CHEN, Wenquan ZHU, Wenbin CHEN, Mr. Li, Peng DONG, Lihong LIN,
Yanfeng LIU, Peng WANG, Wenling ZHANG 07/27/2017 Detailed Information

Valsartan Impurity K.pdf (846 KB)

Ms. Ge:

According to the results of our telephone communication with the Technology Department of Chuannan Plant 1 today, due to the incomplete quenching of sodium azide caused by the separate treatment of irbesartan sodium azide wastewater, there is the frequent occurrence of muffled explosion in the production process, so the Technology Department carried out the technical improvement by which the sodium azide quenching takes place in the unstratified step in the crude irbesartan process. However, after the improvement, there is an unknown impurity of about 0.544% at 26 minutes in the crude irbesartan, and it is the largest impurity in the irbesartan crude product.

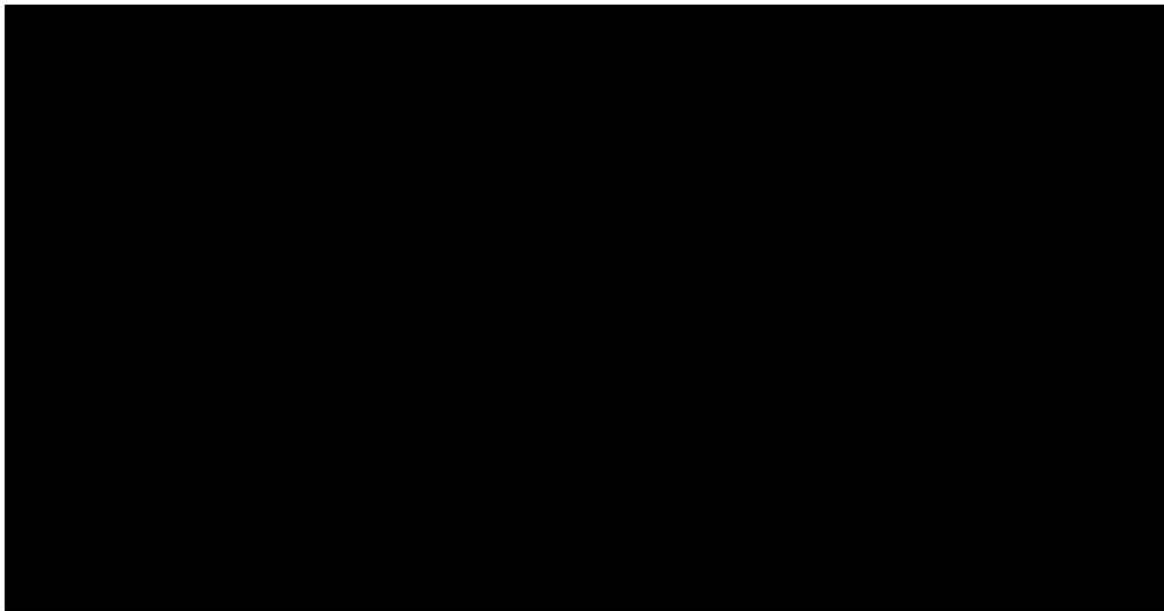
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Min Li
ZHP-296
4/20/2021

Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic. Its possible formation route is shown as follows:



In order to further verify the structure of the impurity and its formation mechanism, we plan to simulate the quenching conditions and use the finished Irbesartan product to react with NaNO_2 and HCl to monitor the impurity produced by the reaction, and then separate it for NMR for final structural verification, while simultaneously carrying out the confirmation of the impurity by multi-stage MS.

If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an extremely high GMP risk. This is a common problem in the production and synthesis of sartan APIs. It is recommended to improve other quenching processes (such as NaClO) along with the optimization of the valsartan sodium azide quenching process.

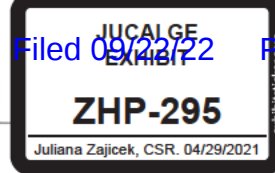
I've also attached a patent of a 2013 sodium azide NaClO quenching method by Zhejiang Second Pharma Co., Ltd. they proposed that the use of NaNO_2 quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude Valsartan in their LC-MS test and detected this impurity. This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue.

Jinsheng LIN

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2017/07/27

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林金生

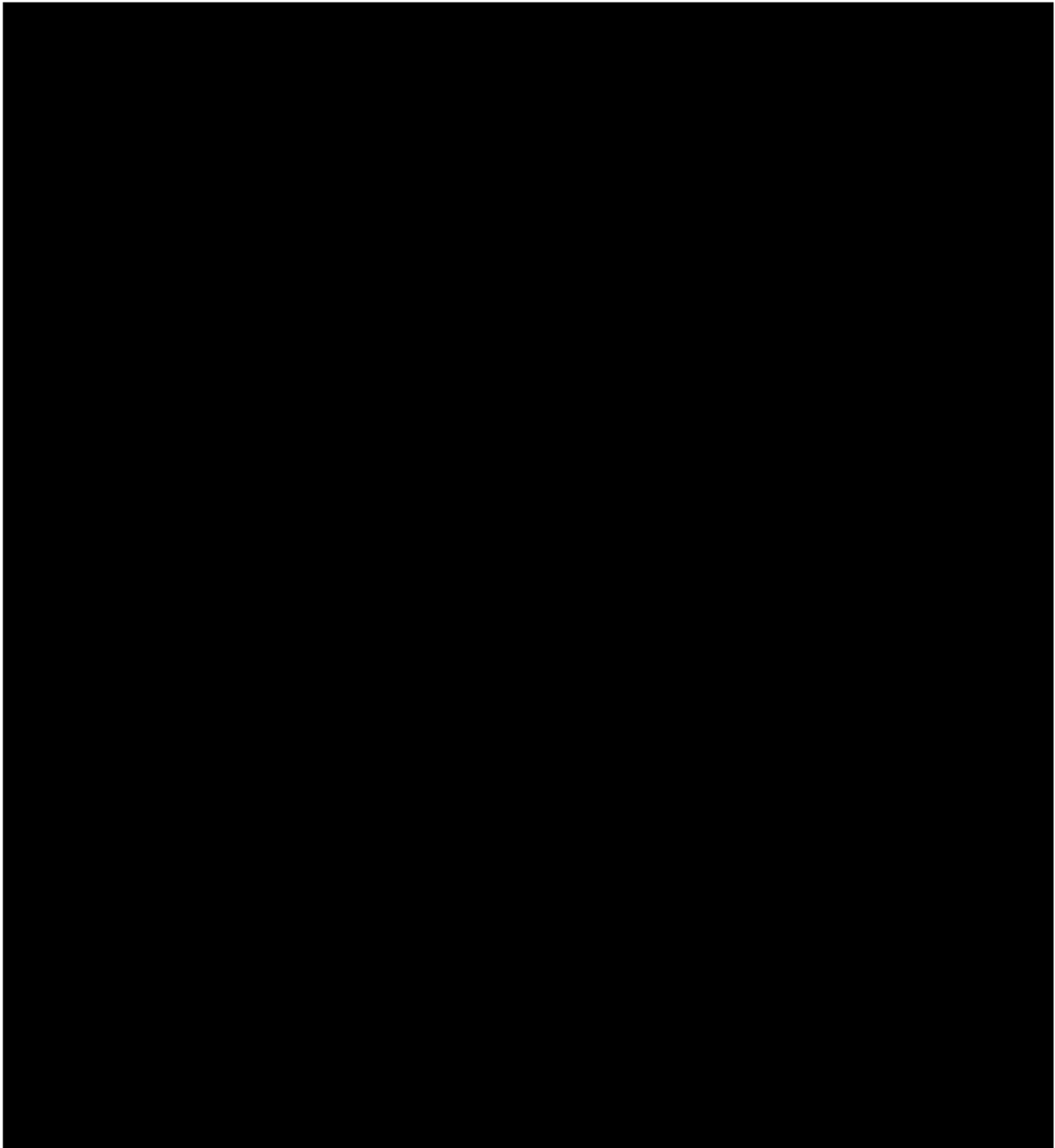
发给 葛菊彩, 黄天培, 陈旺伟, 朱文泉, 陈文斌, 李总, 董鹏, 林丽红, 刘燕峰, 王鹏, 张文灵

2017-07-27 16:17 详细信息

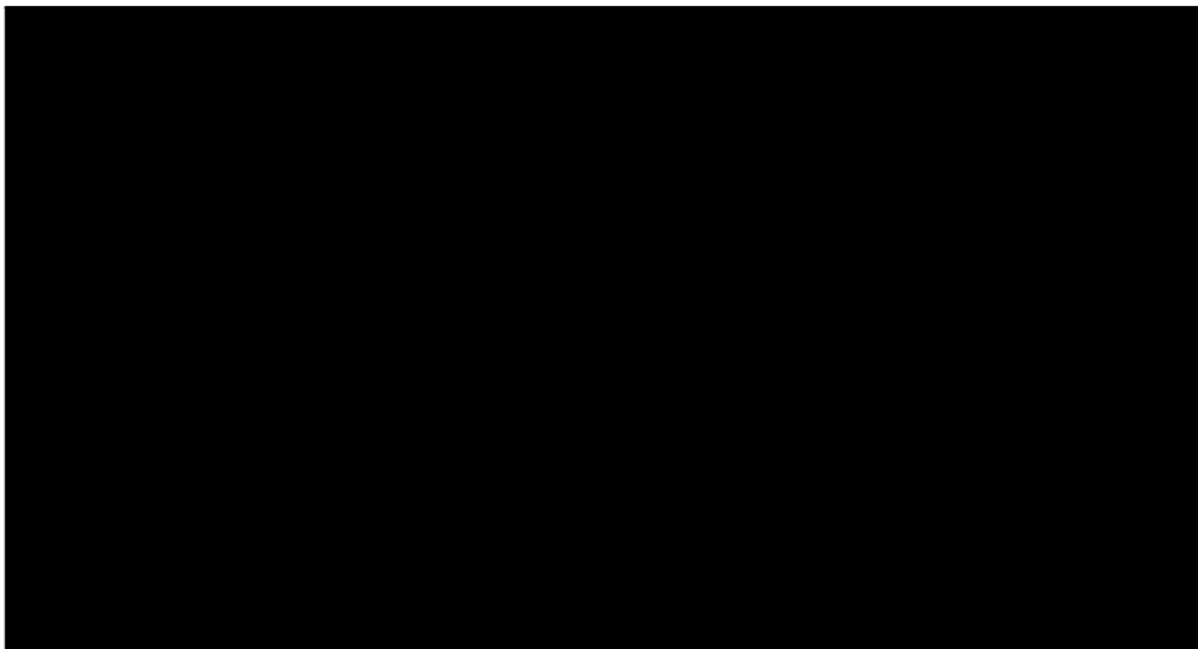
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葛总：

根据我们今天与川南一技术部电话沟通结果，因厄贝沙坦叠氮钠废水单独处理导致叠氮钠淬灭不完全导致生产过程中发生经常性产生闷爆的现象，所以技术部开展了在厄贝沙坦粗品工序未分层工序即淬灭叠氮钠的技改工作,但改进后得到厄贝沙坦粗品中在26min处产生了0.544%未知杂质，并且是厄贝沙坦粗品中的最大杂质。



通过二级质谱分析，可以推测多出的NO₂在环合物片段部分，并且有很大的可能是N-NO化合物，与缬沙坦用亚硝酸钠淬灭产生的N-亚硝基二甲胺相似，其结构具有很强的毒性，其可能产生途径如下：



为了进一步确认该杂质结构及产生的原理，后续我们打算模拟淬灭条件用厄贝沙坦成品与NaNO₂及HCl反应监控反应产生的杂质，再分离出来做NMR进行最终的结构确认，同时同步开展杂质多级质谱的确认工作。

若是确认为上述推测的结构，则其毒性会很强，GMP风险极大，这在沙坦类API生产合成是个共性问题，建议与缬沙坦叠氮钠淬灭工序优化一起，改进其它的淬灭方式如NaClO等。

另附一篇2013年新赛科药业叠氮钠NaClO淬灭方式的专利，他们提出用NaNO₂淬灭会产生N-NO杂质，同时把我们华海的缬沙坦粗品用LC-MS检测的确是发现了该杂质，说明其他企业很早就重视该质量问题了，还请各位领导重视。

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2017/07/27